REMARKS

Status of the claims

Claims 1-69 stand rejected. Claim 35 has been cancelled without prejudice to pursuing it in a continuation application. Claim 36 has been amended without prejudice to presenting it in its original form in a continuation application. Claims 70-73 are new. Support for claims 70-73 may be found, for example, at page 11, line 22 through page 12, line 4 and page 18, line 23 through page 19, line 33.

References not considered

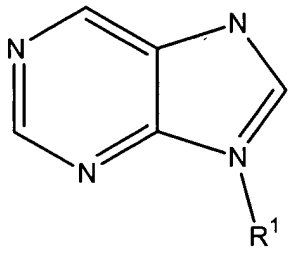
* Enclosed are copies of the post cards submitted with the Information Disclosure Statements of August 18, 1998, October 13, 1998, August 14, 2000, and July 19, 2001, which indicate that copies of the references were submitted with the Statements (with the exception of the August 14, 2000 Statement). Apparently, however, these did not reach the Examiner. Thus, Applicants re-submit copies of all references cited in the Information Disclosure Statements.

35 U.S.C. §112, first paragraph

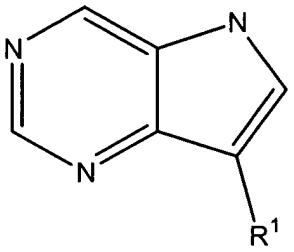
Reconsideration is requested of the rejection of the specification and claims 1-19, 22-31, 35-54 and 58-66 under §112, first paragraph, for lack of enablement. The Office asserts that "Applicant fails to set forth the criteria that defines an 'antiviral compound.'" To the contrary, the application requires the antiviral compounds comprised by the instant application to be "selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof." See Specification, page 6, lines 16-19, and claims 1-16, 19, 22-31 and 35-52. Claims 17 and 53 require a

nucleoside antiviral compound and claims 18 and 54 require a nucleotide antiviral compound.

As described by the application, see page 16, lines 5-21, nucleosides and nucleotides useful in the instant invention are compounds derived from purine bases (II) or pyrimidine bases (III), or from analogs such as compounds IV or V:



II



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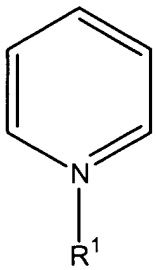
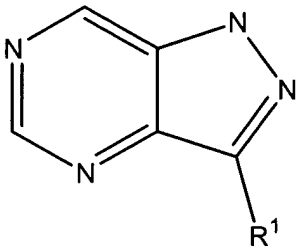


III



V

R^1 can be selected from hydroxyalkyl, hydroxyalkenyl, thiolalkyl, alkylthioalkyl, alkoxyalkyl, alkoxyalkenyl, heterocycle, heterocycloalkyl, hydroxyalkylalkoxyalkyl, alkoxyalkylalkoxyalkyl, and cycloalkylalkyl. The purine or pyrimidine may be further substituted at other positions on the ring(s), see page 16, lines 20-21.

Contrary to the Office's assertion, the claims do not read on all antiviral compounds, but only those antiviral compounds that are nucleosides, nucleotides, or mixtures thereof. The specification provides numerous examples of nucleoside antiviral compounds and nucleotide antiviral compounds, see page 18, line 26 through page 19, line 31. Others would be known to one skilled in the art, and their identification and selection would

not involve undue experimentation. The mere fact that some experimentation may be necessary to select antiviral compounds not named in the specification does not render the specification non-enabling:

> "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'"
> MPEP §2164.06, citing In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The specification and claims 1-19, 22-31, 35-54 and 58-66, do describe the antiviral compounds useful in the invention, and one skilled in the art could make or use the invention without undue experimentation. Thus, the specification and claims 1-19, 22-31, 35-54 and 58-66 satisfy the requirements of §112, first paragraph.

35 U.S.C. §112, second paragraph

Reconsideration is requested of the rejection of claims 1-19, 22-31, 35-54 and 58-66 under §112, second paragraph, as indefinite. The Office asserts that these claims fail to clearly set forth the metes and bounds of the patent protection desired due to reference to "antiviral compounds," and that the specification does not provide criteria that define medicaments that "fall under the 'antiviral compound' penumbra."

MPEP §2173.02 requires that definiteness of a claim be analyzed in light of the disclosure of the instant application, the teachings of the prior art and the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made. The claims refer to antiviral compounds

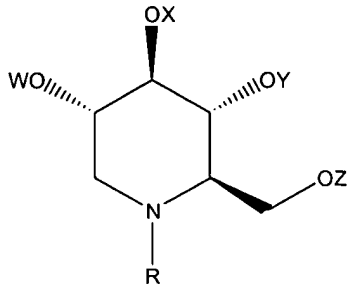
selected from the group consisting of nucleoside antiviral compounds, nucleotide antiviral compounds, and/or mixtures thereof. Nucleosides and nucleotides useful in the instant invention, and methods for their preparation, are discussed in detail at page 16, line 5 through page 20, line 31 of the specification. The phrase "antiviral compound" is well-recognized in the art, and does not require further definition or criteria. One skilled in the art would recognize whether a particular nucleotide or nucleoside compound is an antiviral compound. Thus, in light of the disclosure of the specification, the state of the prior art, and the high level of skill of one of ordinary skill in the art, use of the phrase "antiviral compound" does not render claims 1-19, 22-31, 35-54 and 58-66 indefinite.

35 U.S.C. §102

Reconsideration is further requested of the rejection of claims 35-40, 43-45, and 48-51 under §102(b) as anticipated by Westarp et al. and under §102(a) as anticipated by Chang et al.

Claim 35 has been cancelled without prejudice, rendering its rejection moot.

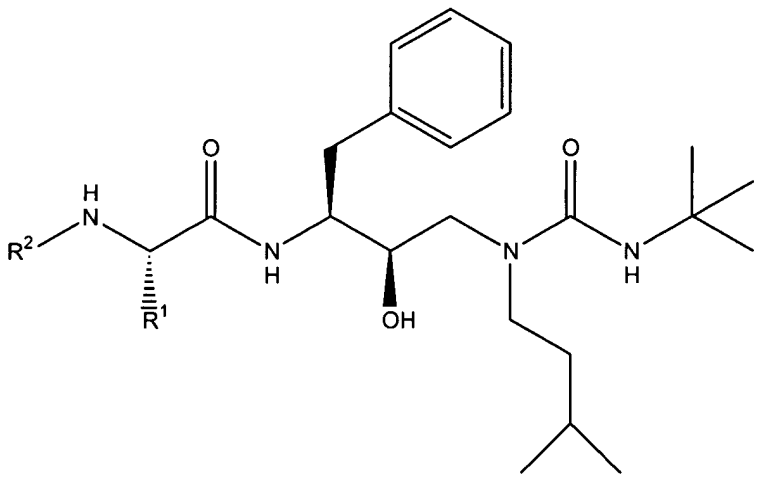
Claim 36, as amended, is directed to a pharmaceutical composition for the treatment of hepatitis infection comprising a first amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol (DNJ) compound of Formula I:



a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof; and a pharmaceutically acceptable carrier, diluent, or excipient.

Westarp et al., German patent No. DE 43 07 883 A1, describe treatment of motor neuronal disorders such as ALS by administration of anti-retroviral compounds (e.g., anti-HIV compounds). Among the numerous classes of compounds disclosed are nucleoside and nucleotide analogues (e.g., AZT and ddI), and the iminosugars DNJ and N-butyl-DNJ. Others include reverse transcriptase inhibitors, isoquinoline protease inhibitors, phosphonoacetic acid analogs, and antidepressants.

Chang et al., U.S. patent No. 5,750,648, describe novel HIV-protease inhibitors and their use in the treatment of HIV infection. The protease inhibitors have the following structure:



wherein R^1 and R^2 are as defined in the reference. In addition, they describe the use of these novel compounds in combination, either as separate compositions or as a single composition, with one or more anti-HIV compounds including nucleoside and non-nucleoside retroviral reverse transcriptase inhibitors, other HIV-protease inhibitors, and glucosidase inhibitors including N-butyl-DNJ and N-butyl-DNJ perbutyrylate.

Hirsch et al., U.S. patent No. 5,011,829 (made of record in the Information Disclosure Statement submitted August 11, 2000 (reference #44)), disclose a pharmaceutical composition containing a synergistic combination of AZT and N-butyl-DNJ for the inhibition of HIV.

None of Westarp et al., Chang et al. or Hirsch et al. anticipate claim 36. None of these references teach a combination of an N-substituted-DNJ and a nucleoside or nucleotide antiviral compound for the treatment of hepatitis infection, as required by claim 36. Additionally, the compositions disclosed by Hirsch et al. are formulated in dosages suitable for treatment of HIV, but not necessarily for treatment of hepatitis virus. For instance, the preferred dosage ranges of N-butyl-DNJ and AZT disclosed by Hirsch et al. encompass dosages that are substantially greater than the preferred dosages of the N-substituted-DNJ compound and antiviral compound of the compositions described in the instant application. Thus, claim 36 is novel in light of the cited references.

Claims 37-40, 43-45, and 48-51, which depend from claim 36, are not anticipated by the cited references for the foregoing reasons, and for the additional requirements which they add.

35 U.S.C. §103

Reconsideration is requested of the rejection of claims 1-69 under §103 as unpatentable over Block et al., Repp et al., Applicants' admissions on the record, and Gish et al.

Block et al. I, Proc. Nat'l. Acad. Sci. USA (1994) 91:2235-2239, disclose that secretion into the culture media of human Hepatitis B virus (HBV) is inhibited by N-butyl-DNJ. Block et al. II, U.S. patent No. 6,037,351, disclose a method of inhibiting HBV using N-alkyl-DNJ compounds in which said alkyl

group contains from 3 to 6 carbon atoms. As background, Block II mentions the use of a nucleoside analog, fialuridine, for treatment of chronic hepatitis B, but reports that clinical tests of this compound have been suspended due to drug-related liver failure in six of the twenty patients studied. See col. 1, lines 41-44. Nowhere do Block I or II suggest a combination of an imino sugar and an antiviral compound selected from nucleoside antiviral compounds, nucleotide antiviral compounds, and mixtures thereof.

Repp et al., J. Biol. Chem. (1985) 260:15873-15879, disclose inhibition of Mouse Hepatitis Virus (MHV) by glucosidase inhibitors such as DNJ and N-methyl-DNJ.

Gish et al., Exp. Opin. Invest. Drugs (1995) 4:95-115, disclose a number of agents for the treatment of chronic HBV infection, including immune modulating agents, vaccines, herbal therapy, nucleoside analogues, synthetic oligodeoxyribonucleotides, antisense molecules and decoys. They present a general discussion of the potential benefits of a combination therapy, and remark that "the future use of immunomodulating agents such as interferon or interleukin with a nucleoside analogue appears promising." However, Gish et al. make no mention of DNJ or N-substituted-DNJ, either alone or in combination with a nucleoside antiviral compound and/or a nucleotide antiviral compound.

The Office asserts that claims 1-69 are obvious in view of the cited references and Applicants' admissions of record, because it is "prima facie obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose." (The Office states that "the instant claims define . . . the concomitant use of two conventional anti-inflammatory agents." Presumably, use of the term "anti-

inflammatory" was unintentional.) Applicants respectfully submit that there is no basis in the art for this conclusion, that any general discussion of combination therapy fails to render obvious the particular combinations claimed herein, and thus that the Examiner has effectively slipped into an improper "obvious to try" analysis, informed by hindsight which Applicants' disclosure affords.

One skilled in the art would view the anti-hepatitis agents disclosed separately in the references as alternatives to one another, sufficient unto themselves for the treatment of hepatitis infection, and thus would not have combined them absent a suggestion within the art to do so, coupled with a reasonable expectation of success. Viewed prospectively, one skilled in the art would have recognized that compounds known individually to be effective in treating a HBV infection could as readily be competitive as complementary when combined in a composition, in which case compositions comprising those compounds would not be effective to treat hepatitis infection.

The actual teachings of the cited references particularly fail to make it obvious to select the N-substituted-DNJ compounds and the nucleoside or nucleotide antiviral compounds, out of the many agents that individually show activity against HBV (see, e.g., Gish et al.). Among the many compositions proposed in the art for treatment of hepatitis infections, the cited references offer no guidance which would have enabled one skilled in the art to select N-substituted-DNJ compounds for combination with nucleosides or nucleotides. Obviousness must be assessed against the entire background of the art, *see* In re Kuderna, 165 USPQ 575, 578-79 (CCPA 1970). If anything, Block II tends to distance N-substituted-DNJ compounds from nucleosides, inasmuch as it teaches therapy with the former alone, while recounting unfavorable experiences with the latter.

Applicants, on the other hand, selected N-substituted-DNJ compounds and nucleoside or nucleotide antiviral compounds from the many antiviral compounds known in the art, chose further to administer them in combination, formulated a composition comprising the same, and have demonstrated the efficacy of the combination therapy for inhibiting hepatitis virus, see Specification, Example 3. Furthermore, they have included compounds not disclosed in the cited art for treatment of hepatitis infections, e.g. DNJ compounds that are substituted at the nitrogen by alkyl groups of greater than six carbon atoms, as well as DNJ compounds with functionality at the hydroxy groups.

In support of its position that claims 1-69 are obvious, the Office cites In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). In Kerkhoven, Appellant claimed a process for the production of particulate detergent compositions containing a mixture of anionic detergents and nonionic detergents. Kerkhoven, 626 F.2d at 848. The Examiner rejected Appellant's claims as obvious, stating the claims required no more than the mixing of two conventional spray-dried detergent compositions to form a third composition for the same purpose. Id. at 849. The CCPA affirmed the rejection, holding that it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, to form a third composition to be used for the same purpose. Id. at 850. According to the court, the motivation to combine the compositions "flow[ed] logically from their having been individually taught in the prior art." Id.

Claims 1-69 may be distinguished from Kerkhoven. In Kerkhoven, there was no reason to expect that the combination of detergent compositions could act differently from the individual compositions comprising it, and thus it would have been obvious to one skilled in the art to combine them for their additive effects as detergents. While this may be the case in the

detergent arts, the same cannot be said about the pharmaceutical arts. Claims 1-69 disclose compounds that are combined for their physiological effect, namely treatment of hepatitis virus infections. The combined physiological effect of the compounds would not have been obvious to one skilled in the art. A skilled artisan would have recognized that compounds known individually to be effective in treating a hepatitis infection could possibly compete with one another when combined in a composition, in which case compositions comprising those compounds would not be effective to treat hepatitis infection. Furthermore, there is a lack of motivation in the art to select N-substituted-DNJ compounds for combination with nucleosides or nucleotides. Thus, claims 1-69 are not obvious in view of the cited references.

Lastly, the Office maintains that it would have been obvious to "employ an analog, homolog, isomer, bioisostere, salt, acid or ester" of a known compound for the same use, and that the prior art teaches N-alkyl-DNJ derivatives for treating hepatitis. Contrary to the Office's assertion, Block et al. do not teach N-alkyl-DNJ derivatives generally. Block I refers only to N-butyl-DNJ, and Block II is limited to alkyl groups with three to six carbon atoms. Repp et al. teach only N-methyl-DNJ as an inhibitor of MHV. In any event, disclosure of certain N-alkyl-DNJ derivatives as inhibitors of hepatitis virus does not render obvious the compositions and methods of the instant application, for the reasons given above. The art neither suggests the use of N-substituted-DNJ compounds in combination with nucleosides or nucleotides to treat hepatitis infection, nor provides any reasonable basis for expecting that the combination would offer any benefit or advantage.

Supplemental Information Disclosure Statement

Submitted with this Letter is a Fourth Supplemental Information Disclosure Statement and copies of the references cited therein, for consideration by the Patent and Trademark

Office in the above-entitled application and to be made of record therein.

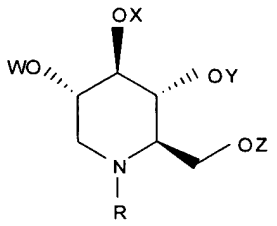
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 35 has been cancelled.

Claim 36:

36. (Once amended) A pharmaceutical composition **for the treatment of hepatitis infection**, comprising a first amount of an *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I:



wherein:

R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of C_1 to C_{20}, and

W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl; and

a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and

a pharmaceutically acceptable carrier, diluent, or excipient.

Claims 70-73 are new.

Conclusion

In view of the foregoing remarks, it is respectfully submitted that the specification and claims 1-69 meet all requirements of 35 U.S.C. §112, and that claims 1-69 are patentable over the art of record under 35 U.S.C. §§ 102 and 103(a). Favorable reconsideration and early allowance of all claims are respectfully requested.

The Commissioner is hereby authorized to charge any fees required under §1.17 or refund any overpayment to Deposit Account No. 19-1345.

Respectfully submitted,

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(390)

MISCELLANEOUS

Attorney JKR

File SRL 62067

Client Name C.P. Searle

Inventor(s) or Mark Gary S. Jacob

Serial No. 09/023,701 Patent/Reg. No.

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MISCELLANEOUS (390)

File SRL 6067 Attorney CEC/lep

Client Name G.D. Searle & Co.

Inventor(s) or Mark Jacob, et al.

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MISCELLANEOUS (390)

File SRL 6067 Attorney CEC/sdl

Client Name G. D Searle & Co.

Inventor(s) or Mark Gary S. Jacob et al.

Serial No. 09/023,401 Patent/Reg. No. N/A

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OIPE JC16 APR 02 2002 PATENT & TRADEMARK OFFICE

MISCELLANEOUS (390)

File -SRL 6067 Attorney JKR

Client Name Searle

Inventor(s) or Mark Jacob et al.

Serial No. 09/023,401 Patent/Reg. No. _____

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